

New Drugs for *Clostridium difficile* Infection

John G. Bartlett

Johns Hopkins University School of Medicine, Baltimore, Maryland

(See the article by Louie et al. on pages 411–20 and the article by Musher et al. on pages 421–7)

Clostridium difficile was originally defined as the cause of antibiotic-associated colitis in 1978. Subsequent studies have provided a nearly complete portfolio of information on the pathophysiology and management of this complication. This clinical syndrome has a known cause (toxins A and B of *C. difficile*), established risks (age, hospitalization, and antibiotic exposure), good diagnostic tests (stool cytotoxin assays), and effective treatment (oral metronidazole or vancomycin). During the past few years, there has been renewed interest in *C. difficile*, reflecting the recognition of a form of disease that is more frequent, more severe, and more refractory to standard treatment [1]. It now appears that these observations are explained by the presence of a new strain of *C. difficile*, designated NAP-1, that produces more toxin A and B in vitro [2], produces binary toxin that is of uncertain significance [3], and is resistant to fluoroquinolones, which may account for the surge in cases [4].

Treatment of *C. difficile*-associated disease has traditionally been to discontinue the implicated agent and, for those patients who have at least moderately severe

or persistent disease, to give oral metronidazole or oral vancomycin. Prior experience with these drugs shows that they are generally effective for acute disease, but treatment is often complicated by recurrences after treatment. Our experience with 189 patients, including 100 with endoscopy-proven pseudomembranous colitis, showed that 96% of the patients responded to oral vancomycin, but 24% experienced relapses when vancomycin therapy was discontinued [5]. Other studies have reported a similar experience [6].

The relative merits of oral vancomycin and metronidazole for treatment of acute disease are debated. Metronidazole is favored by the Centers for Disease Control and Prevention, the Society for Healthcare Epidemiology of America, and the Infectious Disease Society of America [7] on the basis of cost, the results of clinical trials showing therapeutic equivalence with vancomycin [8, 9], and the possibly erroneous impression that metronidazole is less likely than vancomycin to promote colonic colonization with vancomycin-resistant enterococci [10]. Vancomycin enthusiasts argue that vancomycin has ideal pharmacologic properties, that it is the only drug approved by the US Food and Drug Administration (FDA) for this indication, and that it appears to be better than metronidazole in some clinical trials in terms of response rates and time to pathogen or toxin eradication [11–13]. The relevant pharmacology issues concern the fact that *C. difficile* is completely re-

tained in the colon lumen; it does not invade the colon mucosa or cause bacteremia. Thus, the ideal antibiotic is one that is concentrated in the colon, shuts down toxin production, and is always active against *C. difficile*. Vancomycin has these characteristics. This drug is not absorbed when given orally; therefore, it reaches levels in the colon lumen that are 50–200-fold higher than the MIC, and resistance has never been reported [14]. By contrast, oral metronidazole is well absorbed; therefore, colonic levels are below detection, except the presence of diarrhea [14, 15]. This has led to the conclusion by many that oral vancomycin is the preferred drug for patients who are seriously ill or who fail to respond rapidly to metronidazole treatment [16–18]. In fact, on the basis of pharmacology and clinical experience, it is hard to think of an antibiotic that is likely to be more effective than vancomycin for the treatment of acute disease.

The main problem with managing acute disease in the past has been ileus or other concurrent conditions that preclude oral treatment. Such cases have been relatively rare, but, when encountered, they required creative methods to get vancomycin to the site of action, usually by means of long tubes placed from above (nasogastrically) or below (colorectally) [19].

The other therapeutic challenge has been the frequency of relapses after treatment is discontinued, which is a problem seen in 20%–25% of patients. This event occurs with

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Reprints or correspondence: Dr. John G. Bartlett, Johns Hopkins University, School of Medicine, 1830 E. Monument St., Rm 439, Baltimore, MD 21287 (jgb@jhmi.edu).

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almost equal frequency among patients receiving vancomycin and those receiving metronidazole [5, 8, 9, 13]. Most patients respond to treatment with either drug, but the recurrence rate with retreatment is higher than with the initial course of therapy, and some patients continue to have recurrent disease [20]. The clinical features are highly characteristic; patients respond well while taking metronidazole or vancomycin, but they experience a recurrence of the same symptoms after therapy is completed (usually 1–10 days after treatment is discontinued) [20]. Patients who have repeated recurrences often take repeated courses of metronidazole or vancomycin to control the disease or take continuous vancomycin to avoid recurrences. In my personal experience, I have treated 1 patient who experienced 26 recurrences and 3 other patients who received continuous vancomycin therapy for 2 years. The cause of recurrent disease is either a true relapse involving the same strain of *C. difficile* that was responsible for the first episode or a reinfection involving a new strain [21]. Thus, there is a paradox in that these 2 antimicrobial agents both cause and cure *C. difficile*-associated colitis. The same paradox is seen with the hamster model. Clindamycin causes lethal *C. difficile* colitis in hamsters; they can be saved with oral vancomycin, but will die because of *C. difficile* colitis when vancomycin is discontinued. Also, vancomycin alone may serve as an inducing agent [22, 23].

There are multiple methods to treat recurrent disease, including probiotics [24], fecal implants [25], anion-exchange resins to absorb toxin [26], immune therapy with intravenous immunoglobulin [27], *Saccharomyces boulardii* [28], and vancomycin with tapering doses or pulse doses [29]. The only treatment listed that has established efficacy in a clinical trial is treatment with *S. boulardii* [28], although these results were not sufficiently convincing for FDA approval. The best-reported experience is with fecal implants and pulse doses of vancomycin [25, 29], but the number of reported cases is small,

and trials are uncontrolled. There are other problems, such as availability and expense of intravenous immunoglobulin, the aesthetic and liability issues with fecal implants, and very limited data or poor outcomes shown with anion-exchange resins and probiotics. It can be safely concluded that all of these treatments work some of the time, none work all of the time, and clinicians have no data-driven guidance (including any guideline from an authoritative source) that addresses the issue of managing multiple recurrences.

The NAP-1 strain has forced a closer look at current therapeutic options, in part because *C. difficile*-associated colitis now seems to be more common and severe, but also because it appears to be more refractory to standard therapy [1, 17, 30]. Specifically, the “Quebec experience” includes reports of an attributable mortality rate of 17% [31] and a total of >1400 deaths in Quebec, Canada [32], which is 30 times the number of deaths attributed to severe acute respiratory syndrome in Toronto, Canada. Also, the rate of recurrent disease in patients >65 years old is reported to be at a record high of 58% [33]. Thus, this new strain appears to place new emphasis on old problems with treatment.

The implication of these observations is that there is a need for new therapies. The challenge of new therapy for acute disease in seriously ill patients is particularly difficult, based on the pharmacologic properties and predictable in vitro activity of vancomycin. An exception is the need for alternatives to oral agents for patients with ileus. The need for new therapy to prevent relapses must be a high priority, because the problem is common, the current selection of treatments is inadequate, and the relative merits of these treatments are not known. It should be emphasized that the needs for managing acute disease and recurrent disease appear to be different. For acute disease, the need is a treatment that can address the problem of patients with overwhelming toxin-induced disease and the problem of patients for

whom it is not possible to get oral vancomycin to the colon lumen. The comparator drug needs to be vancomycin. For recurrent disease, the need appears to be to control *C. difficile* after completion of apparently successful treatment. A possible third need is for an alternative to vancomycin or metronidazole, for the patient who is neither seriously ill nor experiencing recurrent disease. Here, the need is for a drug that is associated with some defined advantage, such as reduced cost, better tolerance, lower recurrence rate, and/or less deleterious impact on nosocomial pathogens.

This issue of *Clinical Infectious Diseases* has 2 reports of new agents for treatment of *C. difficile*-associated enteric disease. One agent is nitazoxanide, which is a nitrothiazolidine marketed for treatment of intestinal parasites, but which also has desirable properties that include in vitro activity against *C. difficile* [34] and high colonic levels with oral administration [35]. Studies using the hamster model have shown that, unlike metronidazole and vancomycin, nitazoxanide does not induce *C. difficile*-associated colitis [34]; however, the rate of recurrent disease was similar to that associated with metronidazole therapy and was higher than that associated with vancomycin therapy [34]. The first report of this agent for treatment of *C. difficile* infection in people is a report by Musher et al. [35], a randomized, double-blind trial comparing metronidazole administered at a dosage of 250 mg 3 times per day for 10 days, nitazoxanide administered at a dosage of 500 mg 2 times per day for 7 days, and nitazoxanide administered at a dosage of 500 mg 2 times per day for 10 days. Results showed that nitazoxanide was “not inferior” to metronidazole in terms of primary response rate or rate of recurrent disease. The data for recurrences showed a trend toward better outcome for patients receiving the 10-day course of nitazoxanide, compared with those receiving the 7-day course (58% vs. 74%), but these results were not statistically significant ($P = .3$). On the basis of

cost and experience, nitazoxanide does not appear to be justified for initial treatment, but it might be used for patients who fail to respond to metronidazole therapy, who cannot take metronidazole, or who have repeated recurrences. It is available in the United States at an average wholesale price of ~\$240 for the 10-day course. Nitazoxanide is not approved by the FDA for this indication, but neither is metronidazole.

The second drug reported in this issue of *Clinical Infectious Diseases* for treatment of *C. difficile* infection is tolevamer [36], a nonantibiotic anionic polymer that binds *C. difficile* toxins A and B to neutralize biologic activity in vitro and in rabbit ileal loops [37]. This mechanism of action is similar to that of anion-exchange resins, such as cholestyramine, which were ineffective in the hamster model [23] and in a clinical trial [38]. However, studies of tolevamer in the hamster model showed that this drug prevented clindamycin-induced lethality, as did metronidazole; but, unlike hamsters that received metronidazole, the hamsters that received tolevamer survived after the drug was discontinued [37]. This suggests that tolevamer may potentially be used to prevent relapses, which is rational, because it represents a non-antibiotic treatment. The important difference between tolevamer and cholestyramine may be the relative merits of these drugs with respect to their affinity for *C. difficile* toxins [37, 39]. The first clinical trial of tolevamer was a multicenter, randomized, double-blind trial comparing tolevamer (administered at a dosage of 1 g 3 times per day or 2 g orally 3 times per day for 14 days) with vancomycin (administered at a dosage of 125 mg orally 4 times per day for 10 days). The results showed that tolevamer administered at a dosage of 6 g per day was “not inferior” to oral vancomycin with respect to initial response as determined on the basis of time to normal stool pattern (which occurred in 83% and 91% of patients, respectively) and with respect to recurrence (which occurred in 10% and 19% of patients, respectively) [36]. Neither differ-

ence in outcome is statistically significant, but there is a trend toward faster response with vancomycin therapy and fewer recurrences with tolevamer therapy. It makes sense that vancomycin would produce a better therapeutic response and tolevamer would be associated with fewer relapses. Louie et al. [36] note that the response was dose related and plan to conduct phase III trials of a 9-g-per-day regimen. Unlike nitazoxanide, tolevamer is not available in the marketplace; therefore, clinicians will not have access to this drug until completion of the phase III trial, which means that the drug will not be available for several years.

There is only 1 therapeutic trial that has led to FDA-approval of a drug for treatment of *C. difficile* infection, which was a placebo-controlled trial with oral vancomycin reported in 1978 [40]. Nearly 30 years later, there are multiple drugs in the pipeline, which include not only tolevamer and nitazoxanide but also ramoplanin (Oscient Pharmaceuticals; phase III), OPT-80 (Optimer Pharmaceuticals; phase III), rafalazil (ActivBiotics; phase II), a toxoid vaccine (Acambis; phase I), and monoclonal antibodies to toxin A and toxin B (Medarex; phase II). It seems clear that the frequency of *C. difficile* infections, combined with the therapeutic need, is producing a moderately rich pipeline.

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